Remarks

In response to the Final Action of November 30, 2009, Applicants enclose a response and a sIDS. A Notice of Appeal was filed on May 25, 2010. By virtue of the filing of a Request for Continued Examination submitted herewith, the enclosed response is entered into the application. Favorable consideration of this application is respectfully requested in view of the following remarks.

Claims 10-13 are pending in the application. Claim 10 has been withdrawn from consideration. Claims 11-13 have been rejected.

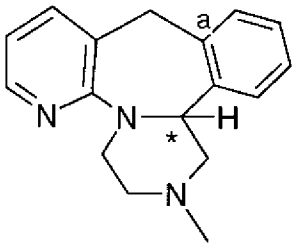
Claims 11-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,062,848 (van der Burg) in view of Pizey, Synthetic Reagents, Volume 6, 1985, pp. 270-275 and pp. 372-414 (Pizey) and Collins, Methods for Obtaining Optically Active Compounds, Chirality in Industry, 1192 (Collins).

Applicants traverse this rejection and respectfully submit that the combination of van der Burg/Pizey/Collins does not make obvious the presently claimed method.

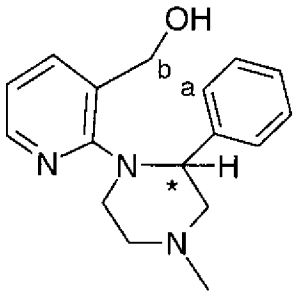
Van der Burg describes preparation of racemic mirtazapine by ring closure using concentrated sulfuric acid. Van der Burg also indicates that pure enantiomers of mirtazapine may be obtained by using enantiomerically pure starting material for the last ring closure step (see column 6, lines 48-60). WO00/62782 (WO'782) also describes that concentrated sulfuric acid is most preferred for the ring closure step (see WO'782, page 7, lines 6-12). However, as stated in the present specification on page 2, the method described in WO'782 with sulfuric acid does not sufficiently retain optical purity. Indeed, those reaction conditions allow for excessive racemization. None of the cited references address the problem of racemisation during reaction when starting from enantiomerically pure material.

Although the use of polyphosphoric acid (PPA) is offered in the art as an alternative to sulfuric acid, it is not obvious to the person skilled in the art seeking to obtain enantiomerically pure mirtazapine to test the reaction on an enantiomer of the compound of formula II, using PPA or phosphorus acid and arrive at the presently claimed method.

The position taken in the Office Action is based on a presumption on the behavior of the skilled person in the field which presumption is not plausible. As shown in formula 1 below, it can be seen that the asymmetric centre (marked with asterix *) is remote from the atoms that make a bond (marked a and b in formula 2) by the reaction induced by concentrated dehydrating acid, such as sulfuric acid.



Formula 1



Formula 2

Faced with the problem of excessive racemisation with sulfuric acid the skilled person would not be in a position to clarify the situation. When trying to ascribe the loss of asymmetry to the acidic reaction conditions by investigating the end product's behaviour under various acidic conditions, a skilled person would have to conclude that it is not caused by instability of the end product. Attempts in the laboratory of the inventor of the present invention have shown that an enantiomer of mirtazapine is stereochemically completely stable in concentrated sulfuric acid. The skilled person might therefore believe that the acidic reaction conditions are such that rearrangement occurs during reaction as a result of the reaction mechanism resulting in excessive loss of asymmetry, even though it is difficult to think of an actual mechanism for racemisation. In view of the lack of a clear explanation, the skilled person will conclude that the type of reaction, the Friedel Crafts reaction, will not have the suitable mechanism of reaction to preserve the asymmetric centre. When faced with the racemisation with this reaction the skilled person will not expect that changing the reaction conditions would improve the situation. Thus, it seems unavoidably that the very mechanism of the Friedel-Crafts reaction is causing the loss of asymmetry and therefore the skilled person will

abandon the attempt to use this type of reaction and either look for another reaction path or stick to separation of enantiomers in order to obtain the pure enantiomer. Only, if there were preservation of the asymmetric centre and the yield would be unsatisfactory, the average skilled person might have considered to further optimize the reaction by exploring other reaction conditions. If at all the skilled person would test another acid, such as PPA, he would be confirmed in his expectation that the reaction mechanism is unsuitable for stereoselective synthesis, because only after further optimisation to specific proportions of reactants or the use of solvents, he would find the solution to the problem. Therefore, the presently claimed invention does not emerge from a straightforward routine optimization of an obvious reaction mechanism. Accordingly, the selection of PPA in the recited ratio would not have been predictable to one of skill in the art, and thus the claimed method would not have been obvious over the combination of van der Burg, Pizey and Collins.

Further, as indicated in the Written Opinion for the corresponding PCT application (see supplemental IDS), in using the specific acid in a specific weight ratio to the compound of formula II or specific acid and organic solvent in combination as recited in claims 11-13, high enantiomeric yields are observed (see Examples 1-3 of the present specification in which improved enantiomeric yields of 99-99.7% were obtained), which high enantiomeric yields are not evident from the cited art.

In view of the above, withdrawal of the rejection of claims 11-13 under 35 U.S.C. §103(a) is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below.

Dated: September 24, 2010

Respectfully submitted,

By _____

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